REMARKS

Claims 44-61 and 63-71 presently appear in this application, with claims 60 and 61 being withdrawn by the examiner. No claim is allowed, although claims 45-48, 55, 56, 58 and 63-68 have been indicated to be allowable if rewritten in independent form. Reconsideration and allowance are hereby respectfully solicited.

The objection to claim 69 is made moot by the amendment to claim 69. Applicants believe that the rejections discussed below are obviated in view of the 1.131 declaration attached hereto and the arguments presented below. Accordingly, the objection to claims 45-48, 55, 56, 58, and 63-68 are now also believed to be moot.

Claims 44, 49-54, 57, and 59 remain rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. However, the Examiner's Interview Summary dated October 23, 2003, indicated that this rejection of claim 57 is withdrawn. Following receipt of the Advisory Action of November 20, 2002, the examiner stated, in response to a telephone query, that claim 57 was inadvertently retained in the §112, first paragraph, enablement rejection.

With regard to claims 44, 49-54, and 59, which the examiner finds to be lacking enablement for an analog of G1 protein having no more than ten amino acid residue substitutions in the sequence of SEQ ID NO:2 or 4, applicants respectfully traverse this rejection.

The enablement requirement of 35 U.S.C. §112 is discussed at section 2164 *et seq* of the MPEP. MPEP §2164.01 states that any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The question is whether the experimentation needed to practice the invention is undue or unreasonable. If the invention can be practiced without undue or unreasonable experimentation, the enablement requirement is considered to be met. The undue experimentation factors of In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) are set forth at MPEP §2164.01(a). These factors include:

(a) the breadth of the claims;

(b) the nature of the invention;

(c) the state of the prior art;

(d) the level of one of ordinary skill;

(e) the level of predictability in the art;

(f) the amount of direction provided by the inventor;

(g) the existence of working examples; and

(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the examiner takes the position that the scope of the claims is broader than the enabled disclosure for analogs thereof.

With respect to the breadth of the claims, part (c) of claims 44 and 54 now specifies that the analogs have no more than ten changes in the amino acid sequence with each such change being a substitution, deletion or insertion of a single amino acid. It further specifies that the analog must bind to MORT-1 and/or MACH. It should be noted that the amino acid sequence of SEQ ID NO:2 has 480 residues, and the amino acid sequence of SEQ ID NO:4 has 221 residues. Thus, ten changes in the 480 residue sequence amounts to only 2%, i.e., the claimed analogs have a minimum of about 98% identity to the specified sequence. Ten out 221 is still about 95% identity for SEQ ID NO:4.

The examiner's attention is invited to the Revised Interim Written Description Guidelines Training Materials, which have been published by the Patent and Trademark Office, Example 14 "Product by Function". There, a claim to a specific sequence and variants thereof that are at least 95% identical thereto and have a specified function was held to comply with the written description requirement. The Guidelines state:

> The single species disclosed is representative of the genus because all members have at least 95% structural identity with the referenced compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

While these Training Materials relate to written description, rather than enablement, they should be instructive also from the standpoint of enablement to the extent that the Patent and Trademark Office has conceded that, with a claim such as the present, a single example is representative of the entire genus of variants with 95% identity. Thus, this is not a particularly wide breadth for an analog claim.

While claims 44 and 54 are somewhat broader than the G1 isoform of SEQ ID NOs:2 and 4 or the encoding DNA, the claimed scope is necessary in order to reasonably cover the invention. In MPEP §2164.08, relating to enablement commensurate in scope with the claims, the MPEP quotes the following from *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

It should be noted that the definition of analog at claims 44(c) and 54(c) all require that the analogs have the ability to bind to MORT-1 and/or MACH. In view of the stated activity and the direction in the specification, which will be discussed below, and the reasonable breadth of the analogs, the breadth is not unduly broad and the experimentation to find everything within the scope of these claims would not be undue.

The nature of the invention, is such that substantial experimentation is reasonably conducted by those of ordinary skill in the art. The present claims are directed to recombinantly-produced polypeptides and DNA encoding same. Applicants concede that there is not 100% predictability in these fields. However, this does not mean that an applicant must be limited to exemplified embodiments. As long as it is shown that the experimentation to determine what falls within the claim is not undue, the enablement requirement is met. As discussed below, the experimentation is not undue.

As to the state of the prior art, there is no close prior art. The reference cited by the examiner here is not prior art as is discussed below in the §102(e) rejection.

As to the level of one of ordinary skill, inventions involving biotechnology involve a very high level of ordinary skill. Because of this extremely high level of ordinary skill, even complex experimentation is not necessarily undue or unreasonable.

The next two *Wands* factors, the level of the predictability in the art and the amount of direction provided by the inventor, go hand in hand. As to the predictability in the art, when changing the sequence by less than 5%, there would be an expectation that the function is maintained. Thus, it is reasonably predictable that such a small number of changes will work, but in any event, it is readily testable in order to determine which will have the claimed function and which will not have the claimed function. The present claim always requires that the result of the amino acid changes have

the ability to bind to MORT-1 and/or MACH, i.e., by definition, the activity must be retained. The specification at page 13, lines 9-12, teaches:

> These two G1α and β isoforms each contain two N-terminal death domain motifs/MORT MODULES and can bind to each other via these death domain motifs, and can also bind to MORT1, MACH and Mch4 via these death domain motifs.

The present specification states at page 33, lines 7-13:

> While any technique can be used to find potentially biologically active proteins which substantially correspond to G1 proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications. The proteins expressed by such clones can then be screened for their ability to bind to various MORT-1-binding proteins, such as, for example, Mch4 and MACH, or even directly to MORT-1, and/or FAS-R and p55-R mediating activity, and/or to mediating activity of any other intracellular pathway in ways noted above.

See also page 36, lines 16-19, where it states:

> When the exact effect of the substitution or deletion is to be confirmed, one skilled in the art will appreciate that the effect of the substitution(s), deletion(s), etc., will be evaluated by routine binding and cell death assays. Screening using such a standard test does not involve undue experimentation.

Furthermore, substantial guidance is provided in the present specification as to preferred substitutions which would be expected to retain the activity of the base compounds, i.e., the G1 proteins. Note, for example, page 33, line 14, through page 36, line 19. Figs. 3A-3C show an amino acid sequence alignment and a comparison of conserved motifs found in human

G1α (hCASHα), human G1β (hCASHβ), mouse CASHα (mCASHα), MACH (CASP-8), and Mch4 (CASP-10). As seen in Figs. 3A and 3B, there is extensive sequence homology in the 1st and 2nd death domain (DED) modules. Thus, one of skill in the art would be fully enabled to make no more than ten amino acid residue substitutions within the death domain modules (based on variations observed at specific residue positions and the guidance in the present specification such as but not limited to pages 33-35 on "conservative" substitutions) and/or within the less conserved regions outside the death domain modules which are not expected to affect the G1 isoforms' capability of binding to MORT1 or MACH.

The examples in the present specification, such as Example 1 (pages 92-97) and Reference Examples 1(i) and (iii), show well-known binding assays, including the two-hybrid screen, two hybrid β-galactosidase expression test, and an *in vitro* binding assay using glutathione agarose beads. These are relatively simple tests. Whole libraries can be screened at one time with the yeast two-hybrid assay. Other binding assays using microarray technology are well known in the art and can test thousands of compounds at once for binding. This is not undue experimentation in this art, particularly in view of the small number of amino acids that may be changed in accordance with the language of the claims. Accordingly, it is apparent that there is substantial direction provided in the specification about how to do these standard binding assays. This is all that is necessary to do in order to determine whether any given analog having no more than ten

amino acid changes has the ability to bind MORT-1 and/or MACH. These minor changes are not unreasonable. Accordingly, substantial direction is provided by the specification.

As far as working examples are concerned, as discussed above, working examples of binding assays are given in the specification and the effect of G1 proteins in these assays is provided in working examples. Human GIα and GIβ isoforms and mouse GIα isoforms shown in Figs. 3a-3c are working examples of analogs for each other. Furthermore, the guidance of the specification explains how to determine whether any given compound falls within the scope of the claims, and therefore additional working examples are not necessary.

Finally, the last *Wands* factor is the quantity of experimentation needed to make or use the invention based on the content of the disclosure. It is true that substantial experimentation will be necessary. However, as stated at MPEP §2164.06, the test is not merely quantitative since a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are not the controlling factors. Procedures for making variants of the G1 protein which have at least 95% identity with the sequence thereof are conventional in the art. See page 33, lines 7-10, where the present specification states:

> While any technique can be used to find potentially biologically active proteins which substantially correspond to G1

> proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications.

The assays involved to determine whether any such analog has the ability to bind MORT-1 and/or MACH are routine, as is disclosed in the specification and discussed above. All of the claimed analogs must possess the specified activity of being able to bind MORT-1 and/or MACH. There is a reduction to practice of the disclosed species of G1 proteins. The fact that any single amino acid change might have a profound effect or no effect, is not really dispositive. Here, standard binding assays are provided in the specification and so any given analog can readily be tested without undue experimentation. Indeed, whole libraries of analogs can be tested simultaneously. Thus, applicants need not rely upon predictability with analogs of respect to changes (even though there is reasonable predictability with analogs of greater than 95% identity), but is relying on testing in the standard assays described in the specification which can be carried out in large numbers at the same time.

The level of skill in the art is high and the assays are standard and can be conducted with many different analog sequences at the same time. Thus, while substantial experimentation may be needed to establish all of the sequences of which fall within the scope of the claim, i.e., meet the functional requirement of binding to MORT-1 and/or MACH, such experimentation is not undue or unreasonable.

Indeed, for any given sequence, the testing is virtually negligible in order to test for binding to MORT-1 or MACH.

For all of these reasons, the enablement requirement is fulfilled with respect to the full scope of claim 54. If there is enablement for the polypeptides of claim 54, there must be enablement for the DNA of claim 44 encoding same and the other claims which depend therefrom.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 44, 49-54, 57, and 70-71 remain rejected under 35 U.S.C. §102(e) as being anticipated by U.S. patent no. 6,242,569. This rejection is respectfully traversed.

The filing date of U.S. patent no. 6,242,569 for purposes of §102(e) is February 5, 1997. Attached hereto is a 37 CFR §1.131 declaration that obviates this rejection because it provides a showing of applicants' conception of the invention on or before the February 5, 1997, filing date of U.S. patent no. 6,242,569, and diligence through to the constructive reduction to practice of the effective filing date of March 3, 1997, of this application. Thus, the present invention was made on or before February 5, 1997, and U.S. patent number 6,242,569 is not available as a reference under 35 U.S.C. 102(e) or 35 U.S.C. 102(e)/103.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting

their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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